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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HADDAD, MAHER M	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 01/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/902,481	MAYO ET AL.	
	Examin r	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 October 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,14 and 29-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *31-33* is/are allowed.

6)☒ Claim(s) *1-7, 14, 29-30 and 34-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a)☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 10/17/03, is acknowledged.

2. Claims 1-7, 14, and 29-39 are pending and under consideration in the instant application.

3. The amendment, filed 11/7/03, is acknowledged to provide a sequence identifier to the sequences on page 29, lines 1-7 under 37 CFR 1.821(d).

4. In view of the amendment filed on 10/17/03, only the following rejections remained.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112.

> *The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.*

5. Claims 1-7, 14, 29-30 and 34-39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant's arguments, filed 10/17/03, have been fully considered, but have not been found convincing.

A. Claims 1, 29-30 and 38 are indefinite and ambiguous in the recitation of "about 98% identical to human integrin I domain" in the claim 1, 2nd line, and "98% identical to the wild-type protein" in claims 29 and 30, 3rd line. Recitation of percentage homology without providing SEQ ID NO for the protein is indefinite and ambiguous because different laboratories may have the same name of a different protein. Further, it is not clear whether the reference protein is derived from human, mouse, rat or other species.

Applicants interpreted the Examiner's comments to mean that the recitation of percent homology without providing a sequence identifier for the *reference* protein and not the *claimed* protein renders the claim indefinite and ambiguous because different laboratories may have the same name for a different protein. Applicants assume that Claims 1, 29, and 30 stand rejected because "human integrin I domain protein" and "wild-type protein" do not have sequence identifiers. Applicants argue that the mode for interpreting claim language during examination requires that "the words of a claim be given their plain meaning unless applicant has provided a clear definition in the specification." M.P.E.P. 21 1 1.01. Applicants contend that by applying this requirement to "integrin I domain protein,". Further, Applicants contends that "integrin l domain" is not indefinite because the term is clearly defined in the specification. In addition, the term "human" further limits the term to integrin I domain proteins of human beings.

Contrary to applicant assertions and explanations, it is indefinite to compare % identity between two molecules without structural features for the comparison.

B. Claims 3-7, 34-37 and 39 are indefinite and ambiguous in the recitation of "substitutions are selected from the amino acid residues at positions selected from positions 139, 153, 156, 157, 160, 199, 215, 219, 223, 238, 239, 240, 259, 269, 271, 299, 308" in claim 3 lines 3-4, " substitutions at positions 156, 160, 199, 215, 238, 239, 240, 259, 269, 271, 287, 299, 308" in claim 4 line 2, " substitutions at position 139, 153, 157, 199, 238, 239, 287, 299" in claim 5 line 2, "substitutions at positions 139, 153, 157, 199, 238, 239, 287, 299" in claim 6, line 2 and " substitutions at positions 215, 219, 223, 238" in claim 7, line 2. Recitation of amino acid positions without providing SEQ ID NO for the protein is indefinite and ambiguous because different laboratories may have different numbering system of the same protein.

Applicants submit that the amino acid positions recited in the claims are set forth in the specification. Applicants concluded that each position is clearly defined in the specification.

Contrary to Applicants assertions recitation of amino acid positions without providing SEQ ID NO for the protein is indefinite and ambiguous because different laboratories may have different numbering system of the same protein.

C. Claim 38 is indefinite for reciting "less than about" in line 2. It is unclear how what percentage constitutes "less than about". One of skill in the art would not know if applicant meant 1%, as many as 50%, or even more.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-7, 14, 29-30 and 34-39 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a non-naturally occurring integrin I domain protein of SEQ ID NOS: 3 (ido1q), 4 (ido1r) and 5 (ido2r) for stabilizing the integrin I domain in the open conformation and SEQ ID NO: 6 (jlm2r) for close conformation, and a composition thereof does not reasonably provide **enablement** for any structurally biased "integrin I domain protein" comprising an amino acid sequence that is less than 98% identical to human integrin I domain protein wherein the alterations to the protein occur in at least two noncontiguous regions wherein said integrin I domain protein is artificially biased to exist in a "open" conformation in claim 1, any full length integrin comprising the said domain in claim 2, any non-naturally occurring integrin I domain protein comprising at least 4 amino acid substitutions, wherein at least 2 of said substitutions correspond to positions of human alpha-M I domain protein selected from the group consisting of 139, 153, 156, 157, 160, 199, 215, 219, 223, 238, 239, 240, 259, 269, 271,

299 and 308 in claims 3-7; a pharmaceutical composition comprising an integrin I domain protein according claim 1, 2, or 3 and a pharmaceutical carrier in claim 14 or a composition comprising "any integrin" that is artificially biased to exist in the open/closed conformation, where the artificial bias is a result of noncontiguous alteration of the protein, these alterations results in a protein that is less than 98% identical to the "wild-type protein", crystallized with "a ligand" in claims 29/30, a non-naturally occurring integrin I domain protein comprising amino acid substitutions at positions corresponding to positions 156, 160, 199, 215, 238, 239, 240, 259, 269, 271, 287, 29, and 308 of the human alpha-M I domain protein in claim 34, a non-naturally occurring integrin I domain protein comprising amino acid substitutions at positions 156, 199, 215, 238, 239, 240, 259, 287, and 299 of the human alpha-M I domain protein in claim 35, a non-naturally occurring integrin I domain protein comprising amino acid substitutions at positions corresponding to positions 139, 153, 157, 199, 238, 239, 287, and 299 of the human alpha-M I domain protein in claim 36, a non-naturally occurring integrin I domain protein comprising amino acid substitutions at positions corresponding to positions 215, 219, and 238, of the human alpha-M I domain protein in claim 37, A structurally biased integrin I domain protein comprising an amino acid sequence that is less than about 98% identical to human integrin I domain protein wherein the alterations to the protein occur at core positions in at least two noncontiguous regions wherein said integrin I domain is artificially biased to exist in an "open" conformation in claim 38, wherein in said core positions correspond to positions of the human alpha-M I domain protein selected from the group consisting of 139, 153, 156, 157, 160, 199, 215, 219, 223, 238, 239, 240, 259, 269, 271, 287, 299, and 308 in claim 39. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim for the same reasons set forth in the previous Office Action mailed 7/15/03.

Applicant's arguments, filed 10/17/03, have been fully considered, but have not been found convincing.

Applicants draw the Examiner's attention that U.S. Patent No. 6,188,965 and 6,403,312. Applicant contends that the '965 patent provides a detailed description and actual experimental exemplification of how to make and test a number of diverse protein variants (GCN4, X repressor, Z1F268, and Gβ1) designed by the computational method of the present invention. Applicants contend that the '312patent provides a detailed description of the computational method used in the invention to pre-screen libraries of beta-lactamase and xylanase. Applicants concluded that these patents illustrate the predictability of the computational method used in the present invention and its ability to allow the routine automated protein design of a large number of proteins, which can be tested for any property. Applicants submit that the amount of direction or guidance presented in the application is sufficient to allow someone of skill in the art to make and use the claimed invention. The PDA™ method, its application to the integrin 1 domain proteins to generate variants, and methods of making and testing have been well described in the specification.

The Examiner agrees with applicant regarding the PDA™ method provides for the quantitative design and optimization of amino acid sequences, using an "inverse protein folding" approach.

However, the claims fail to meet the enablement requirement for the "how to make and use" prongs of the U.S.C 112, 1st paragraph. The broad brush discussion of making and screening up to 98% variants does not constitute a disclosure of a representative number of members. No such variants were made or shown to exist in an open or close conformation. Only the polypeptides of SEQ ID NOs: 3-6 are disclosed. The specification's general discussion of making and screening for variants constitutes an invitation to experiment by trial and error.

Applicant submits that the PDA™ method begins by classifying each amino acid position as a surface, boundary or core residue, and the residue positions are classified as either fixed or variable. For each variable position, a set of amino acid side chain rotamers are chosen, with at least one variable residue position having rotamers from at least two different amino acid side chains. We calculation then proceeds as follows: for each variable position, the energy of interaction of each rotamer with both the template (e.g. anything that is fixed, including the backbone and any fixed residues) and all possible roumers at all variable positions is calculated. This is done using any number of different scoring functions. That is, the scoring functions are each components that can be used to calculate the energy of interaction: based on hydrophobicity, solvation, hydrogen bonding, electrostatics, etc. By screening all possible sequences for each position that can be occupied, a set of optimal sequences for the protein backbone is identified. Applicant concluded that the goal of the PDA™ method is to produce variants in which at least one physical, chemical or biological property of the variant is altered in a specific and desired manner when compared to the wild-type protein.

Again while the PDA™ method provides for the quantitative design and optimization of amino acid sequences, using an "inverse protein folding" approach, the examiner notes that in order to satisfy the U.S.C 112, 1st paragraph, the specification has to teach how to make and/or use the invention, not how to screen to identify the invention. Until the time when the such structurally biased integrin I domain sequences are identified, then one skill in the art can make them, then screen for them for the activity.

9. Claims 1-7, 14, 29-30 and 34-39 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the same reasons set forth in the previous Office Action mailed 7/15/03.

Applicant's arguments, filed 10/17/03, have been fully considered, but have not been found convincing.

Applicant argues that idoiq, ido1r, ido12r and jlm2r each of the disclosed proteins is at least 98% identical to the wild-type protein. Applicants submit that these embodiments meet the claim limitations and, therefore, the written description requirement has been met. Applicant submits regarding "the skilled artisan cannot envision all the contemplated amino acid sequence possibilities recited in the claimed genus" that this is not the proper standard when examining a patent application under the written description requirement. Applicants submit that a

representative number of species are disclosed by the actual reduction to practice of the non-naturally occuring integrin I domain proteins disclosed in the specification. Each of the disclosed proteins fulfill their respective claim limitations. Therefore, Applicants respectfully assert that specification meets the written description requirement of 112, first paragraph.

However, the Examiner notes that the claimed invention which is drawn to a genus may be adequately described if there is a (1) sufficient description of a representative number of species, or (2) by disclosure of relevant, identifying characteristics sufficient to describe the claimed invention in such full, clear, concise and exact terms that a skilled artisan would recognize applicant was in possession of the claimed invention. To satisfy the disclosure of a "representative number of species" will depend on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. "Relevant, identifying characteristics" include structure or other physical and /or chemical properties, functional characteristics coupled with a known or disclosed correlation between function and structure, or a combination of such identifying characteristics sufficient to show the applicant was in possession of the claimed genus. (see Revised Guidelines for the Examination of Patent Applications Under the 35 U.S.C.112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No.4, pages 1099-1111, Friday January 5, 2001).

In the instant case, however, there is no described or art-recognized correlation or relationship between the structure of the invention, the a structurally biased integrin I domain protein the α1, α2, αM, αL I domain of the integrin and their "open" or "close" conformation, the feature deemed essential to the instant invention. Therefore, one of skill in the art would not envisage, based on the instant disclosure, the claimed genus of variants, wherein the variant has less than 98% identical to human integrin I domain, or the human αM I domain protein, which retain the features essential to the instant invention.

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claim 38 is rejected under 35 U.S.C. 102(b) as being anticipated by Huang et al (JBC, 270:19008-19016, 1995, IDS Ref # C22).

Huang et al teaches that mutant E218H/R221K/L224S (noncontiguous alterations) bound to ICAM-1 (open conformation) with nearly wild-type activity. Huang et al further teaches that I235V/T245S/S245K (noncontiguous alterations) mutant binding to ICAM-1 is depressed (close conformation) (see page 19012, I col., 3rd paragraph in particular). The referenced mutants are 98.5% identical (100-(3X198X100) to human integrin I domain because "about" would open the claims to read on the vicinity of 98%.

The reference teachings anticipate the claimed invention.

12. Claims 31-33 are allowable.

13. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad, whose telephone number is (703) 306-3472. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 872-9307.

Maher Haddad, Ph.D.
Patent Examiner
Technology Center 1600
December 19, 2003

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